The predictive value of small versus diminutive adenomas for subsequent advanced neoplasia

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Abstract

Background and Aims: Patients with previous colorectal adenomas are at increased risk of colorectal cancer. Current guidelines for postpolypectomy surveillance intervals treat all tubular adenomas 1 to 9 mm in size with low-grade dysplasia as carrying the same level of risk. We evaluated whether 6 to 9 mm adenomas detected at colonoscopy are associated with greater risk of advanced neoplasia at follow-up compared with baseline 1 to 5 mm adenomas.

Methods: We retrospectively evaluated a colonoscopy database at a single U.S. academic center. Patients with baseline examinations demonstrating tubular adenomas 1 to 9 mm in size with low-grade dysplasia and no advanced adenomas were included. Follow-up colonoscopies were performed at least 200 days later and were assessed for incident advanced neoplasia (cancer, high-grade dysplasia, adenoma ≥10 mm in size or villous elements).

Results: There were 2477 qualifying baseline colonoscopies. The absolute risk of metachronous advanced neoplasia increased from 3.6% in patients with 1 to 5 mm adenomas to 6.9% in patients with at least one 6 to 9 mm adenoma ($p = 0.001$). Patients with 5 or more adenomas one of which was at least 6 to 9 mm had the highest risk of advanced neoplasia at follow-up (10.4%, $p = 0.006$). When only screening colonoscopies were considered, all baseline groups (1-2 adenomas, 3-4 adenomas, ≥ 5 adenomas) with adenomas 6 to 9 mm in size had an increased risk for metachronous advanced neoplasia(ORs, 4.07; 95% CI, 1.50-11.04; OR, 4.91; 95% CI, 1.44-16.75; OR, 4.71; 95% CI, 1.30-17.05, respectively).

Conclusions: Patients with baseline small (6-9 mm) adenomas have an elevated risk of advanced lesions on follow up compared with patients with only diminutive (1-5 mm) adenomas. Postpolypectomy guidelines should consider risk stratification based on small versus diminutive adenomas.

Introduction

Patients with previous colorectal adenomas are at increased risk of colorectal cancer, though compared with the general population the increased risk may be largely confined to those with advanced or multiple (3 or more) adenomas [1-7]. In current postpolypectomy surveillance guidelines [8, 9], patients are considered at higher risk if they have had an advanced conventional adenoma (adenoma ≥10 mm, or with high-grade dysplasia or villous elements), or 3 or more adenomas. High-risk patients are recommended to undergo their next surveillance colonoscopy at a shorter interval compared with those who have only 1 or 2 low risk adenomas (tubular adenomas ≤9 mm in size with only low-grade dysplasia).

ADRs in clinical practice are increasing [10] as a result of increased awareness of the importance of quality on prevention of interval cancers [11, 12], the availability of registries to facilitate ADR measurements [10], guidelines that endorse measurement of ADR [13, 14], and the development of progressively higher-definition colonoscopes as well as add-on devices (eg, mucosal exposure devices) [15]. As a result, an increasingly large fraction of

screening and surveillance populations have very tiny conventional adenomas detected. Patients with even tiny adenomas are assigned to shorter surveillance intervals, which results in increased cost, risks, and inconvenience to patients, with perhaps limited benefit in cancer protection. Further, the effectiveness of postpolypectomy surveillance is limited by marked variability in the quality of performance of the baseline colonoscopy [13, 14]. Currently, postpolypectomy surveillance guidelines do not account for baseline performance or the adenoma detection rate (ADR) of examiners, and generally assume that baseline colonoscopy has uniform performance. Future postpolypectomy surveillance guidelines might be specified to only apply for doctors with ADRs above a certain threshold, or could vary recommended intervals according to ADR. Longer surveillance intervals could be particularly appropriate for doctors with high ADRs and patients with only tiny adenomas.

For these reasons we expect increasing pressure to expand surveillance intervals for patients with tiny adenomas. In this regard, in many postpolypectomy surveillance observational studies, low-risk adenomas include all tubular adenomas 1 to 9 mm in size with only low-grade dysplasia. However, adenoma size is a known predictor of subsequent risk, as has been repeatedly shown for adenomas ≥10 mm in size compared with 1 to 9 mm in size [1-7]. We hypothesized that adenomas 6 to 9 mm in size, often called "small adenomas," could be associated with a greater risk of subsequent development of advanced neoplasia compared with diminutive adenomas (defined as 1-5 mm) in size. Indeed, though most previous studies have lumped 1 to 5 mm and 6 to 9 mm adenomas

together, some studies have suggested that small adenomas are associated with a higher risk of subsequent advanced neoplasia than are diminutive adenomas [16, 17]. In this report, we describe our experience with the risk of subsequent advanced neoplasia in subjects with small versus only diminutive conventional adenomas.

Methods

A database of colonoscopies conducted at a single center (Indiana University Hospital and an associated outpatient endoscopy center) from 1999 to 2016 was used. The database is periodically updated with procedure information and we have reported previously on surveillance findings collected from this database [18]. Briefly, the database contains patient demographics, polyp findings including histology and size and procedure characteristics including indication. Completion of the procedure and bowel preparation quality were added to the database in 2012. Permission to review the database for the current study was obtained from the Institutional Review Board at Indiana University on November 21, 2018. The database at this time consisted of procedures from January 1999 to June 2016.

We identified patients with only diminutive or small adenomas (<10 mm) and categorized them into either having diminutive adenomas or small adenomas and then into 6 groups: 1 to 2 adenomas both ≤5 mm, 1 to 2 adenomas with at least one 6 to 9 mm, 3 to 4 adenomas all ≤5 mm, 3 to 4 adenomas with at least one 6 to 9 mm, 5 or more adenomas all ≤5 mm, 5 or more adenomas with at least one 6 to 9 mm. Polyp size was

estimated by the endoscopist at the time of the procedure. Patients with concomitant serrated lesions at baseline were not excluded.

We excluded patients with inflammatory bowel disease, colon cancer syndromes (familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer, serrated polyposis syndrome), advanced adenomas (≥10 mm tubular adenoma, villous component, high-grade dysplasia) or cancer at or before the baseline colonoscopy. We only included patients who had at least one follow-up examination at our institution at least 200 days later than the baseline colonoscopy.

Outcome measures:

Advanced neoplasia at follow-up was defined as finding a conventional adenoma that was 10 mm or larger, had high-grade dysplasia (HGD) or villous elements or cancer. We also include sensitivity analyses with an expanded definition of advanced neoplasia which considered a sessile serrated polyp (SSP) with cytological dysplasia (CD) or SSP ≥10 mm along with the abovementioned criteria as definition for advanced neoplasia. We also performed subgroup analyses first limiting the sample to screening patients and then limiting the sample to patients who had 1 to 2 adenomas with a follow-up interval falling between 4.5 to 5.5 years.

Statistical analysis

We report demographics, interval to follow-up colonoscopy, and advanced neoplasia at follow-up for each group. Analysis of variance was used for continuous variables and chi-square tests were used for categorical variables. We then assessed the effects of age,

gender, bowel preparation quality, indication for baseline colonoscopy, time to follow-up and our baseline adenoma categories for risk of advanced neoplasia at follow-up using a logistic regression model. We report odds ratios with 95% confidence intervals. All analyses were performed with IBM SPSS Statistics, Version 25 (IBM Corp, Armonk, NY).

Results

Among 34,467 patients who underwent procedures from January 1999 to June 2016, we identified 2,477 patients who only had diminutive or small adenomas at baseline colonoscopy, who never had advanced neoplasia before this examination and also went through a follow-up examination at least 200 days later at one of our institutions (Figure 1). The largest fraction of the baseline cohort had only 1 or 2 diminutive adenomas (66%). The absolute risk of advanced neoplasia at follow-up was 3.6% among patients with only diminutive adenomas compared with 6.9% among patients with at least one small adenoma (71/1,997 vs 33/480, p=0.001) (Table 1). We performed 2 separate logistic regression analyses using different adenoma subgroups (Table 2). The first logistic regression indicated that age and the presence of a small adenoma were risk factors for metachronous advanced neoplasia while gender and time to follow-up colonoscopy were not (Table 2). The fraction of baseline bowel preparations that were excellent or good was 89.2%. In the multivariable analysis, excellent or good preparation at baseline was not associated with advanced neoplasia at follow-up colonoscopy (OR, 0.65; 95% CI, 0.32-1.31; p=0.229; Table 2).

We performed a second logistic regression using more adenoma subgroups (Table 2). In the second analysis there was only minimal difference in the results for age, gender, years to follow-up, bowel preparation quality or indication from the first analysis, and the results are only shown for these factors for the first logistic regression in Table 2. The second logistic regression indicated that age (result not shown) and the subcategories of patients with at least 3 adenomas one of which was ≥6 mm in size predicted advanced neoplasia at follow-up colonoscopy (Table 2).

The absolute risk of metachronous advanced neoplasia was 10.4% (11/106) among patients with ≥5 adenomas at least one of which was a small adenoma (Table 3). Patients who only had 1 to 2 diminutive adenomas had an absolute risk of 3.3% (54/1625) for advanced neoplasia at follow-up.

Sensitivity analysis:

When SSPs ≥10 mm were also considered as advanced neoplasia, the analysis showed similar results (Supplementary Tables 1-4). Similar results were observed when we removed 29 patients who had ≥10 adenomas at baseline colonoscopy (Supplementary Tables 5-8).

Tables 4 and 5 show findings at follow-up colonoscopy according to baseline screening colonoscopies only. When the analysis was confined to baseline screening examinations only, multivariable analyses showed that all subgroups with adenomas 6 to 9 mm had a higher incidence of advanced neoplasia at follow-up compared with 1 to 2 adenomas <6 mm in size, regardless of the number of total adenomas (Table 5).

Tables 6 and 7 show an analysis limited to patients with 1 to 2 baseline adenomas and who had a follow-up examination between 4.5 and 5.5 years. Patients with a small adenoma had a significantly higher risk of advanced neoplasia at follow-up when compared with patients with diminutive adenomas only (OR, 5.23; 95% CI, 1.55-17.68).

Discussion

In this study we describe a single U.S. center experience of the impact of small versus diminutive adenomas at colonoscopy on the risk of advanced neoplasia at follow-up. Among patients with ≥5 adenomas, the risk for advanced neoplasia at follow-up was far greater for patients who had at least one small adenoma when compared with patients with all diminutive adenomas Thus, we found that adenomas in the 6 to 9 mm size range increase the risk of subsequent advanced neoplasia compared with persons who have diminutive adenomas. Our results suggest that caution is appropriate in lumping all 1 to 9 mm adenomas together in postpolypectomy surveillance guidelines [9].

In addition to 6 to 9 mm adenomas predicting subsequent advanced neoplasia compared with having only diminutive adenomas in our entire study population, we also found that the discriminating effect of 6 to 9 mm polyps on subsequent risk of advanced neoplasia was present when only baseline colonoscopies performed for screening were considered. Thus, when only baseline screening colonoscopies were considered, each of the 3 subgroups of adenomas organized by number of lesions (1-2 adenomas, 3-4 adenomas, and ≥5 adenomas) and containing at least one 6 to 9 mm adenoma had a significantly

higher risk of advanced neoplasia at follow-up compared with the subgroup of the same number of adenomas composed of only diminutive adenomas. In fact, the predictive value of 6 to 9 mm adenomas in screening patients was more striking than the same effect for the entire study population. The explanation for this finding is uncertain, but one possibility is that patients undergoing baseline surveillance examinations had previous examinations at other centers that removed high-risk adenoma findings, but of which we were unaware and could not identify from our database. Such patients would remain at increased risk of advanced neoplasia despite an intervening surveillance examination at our center showing only low-risk adenomas [9].

Most previous studies of risk stratification for subsequent advanced lesions based on baseline findings have not stratified lesions 1 to 9 mm in size [1-7]. However, 2 small studies that did stratify risk by small versus diminutive size of adenomas at baseline suggested an increased risk of subsequent advanced lesions in those with small baseline adenomas [16, 17]. Thus, the observations we made here have been made previously.

During the study interval, endoscopists in our group consistently had ADRs above recommended thresholds [19, 20]. Because ADRs have been increasing in recent years [10], we suspect that our results have good generalizability. Our results may not apply in settings where ADRs are low because the absolute risk of advanced neoplasia could be substantially higher even in persons with very low-risk findings (because more high-risk lesions are missed when ADRs are low). Many of the studies that underlie current postpolypectomy surveillance recommendations [10] were performed before the current

emphasis on ADRs and before high-definition colonoscopes were available. Thus, the prevalence of patients with only tiny adenomas may be substantially different in the current study from earlier studies. Indeed, the difference in risk of subsequent advanced neoplasia observed in the current study between baseline small versus diminutive adenomas groups may largely reflect the current study identifying a large and distinct cohort of very low-risk tiny adenomas that were less frequently observed in earlier studies. This suggestion warrants additional evaluation.

Limitations of our study include that it is a retrospective analysis of a prospectively developed and maintained database. The number of patients in certain of the risk groups was small. Nevertheless, the results supporting the predictive value of adenomas in the 6 to 9 mm size range compared with the 1 to 5 mm size range reached statistical significance. ADRs in our unit are likely to be relatively high, which suggests that our findings will be increasingly relevant as detection improves in community-based colonoscopy. Another potential limitation might be that we did not choose to systematically exclude patients with serrated lesions at baseline. Further, we did not present data on the impact of concomitant SSPs at baseline, primarily because our pathology department has not consistently interpreted SSP versus HP over the study interval, as we have twice demonstrated[21, 22]. Finally, polyp size was estimated endoscopically, which may be subject to operator error[23, 24] and terminal digit rounding[25], but these effects are common to postpolypectomy surveillance studies generally.

In conclusion, these data indicate that lumping small and diminutive adenomas together in postpolypectomy surveillance guidelines may create risk for some patients with 6 to 9 mm adenomas and/or increase procedure-related costs and risks for patients with 1 to 5 mm adenomas. We recommend that additional groups evaluate the impact of small versus diminutive adenomas on the subsequent risk of advanced neoplasia in postpolypectomy surveillance cohorts.

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Figure legend:

Figure 1. Patients excluded from the study

Table 1. demographic features and advanced neoplasia at follow-up in patients with diminutive adenomas (1-5 mm) only and patients with at least one small adenoma (6-9 mm) at baseline colonoscopy

	Total	Patients with diminutive adenomas only at baseline colonoscopy	Patients with at least one small adenoma at baseline colonoscopy	*P* value
N	2477	1997	480	
Age, years (SD)	58.6 (9.7)	58.3 (9.7)	59.8 (9.5)	0.002
Male Gender (%)	1382 (55.8)	1083 (54.2)	299 (62.3)	0.001
Time to follow-up examination, years (SD)	4.5 (2.4)	4.6 (2.4)	3.8 (2.2)	<0.001
6 months – 1 year, n (%)	70 (2.8)	49 (2.5)	21 (4.4)	
1-3 years	554 (22.4)	413 (20.7)	141 (29.4)	
3-5 years	884 (35.7)	675 (33.8)	209 (43.5)	
5+ years	969 (39.1)	860 (43.1)	109 (22.7)	
Excellent or good bowel preparation†, n (%)	1552 (89.2)	1242 (90.1)	310 (85.6)	0.014
Indication, n (%)				0.673
Screening	1144 (46.2)	931 (46.6)	213 (44.4)	
Surveillance	767 (31)	614 (30.7)	153 (31.9)	
Diagnostic	566 (22.9)	452 (22.6)	114 (23.8)	
Advanced neoplasia at follow-up, n (%)	104 (4.2)	71 (3.6)	33 (6.9)	0.001
Cancer	4 (0.2)	4 (0.2)	-	
HGD	7 (0.3)	5 (0.3)	2 (0.4)	
VA ≥ 10 mm	11 (0.4)	8 (0.4)	3 (0.6)	
VA< 10 mm	11 (0.4)	7 (0.4)	4 (0.8)	
TA ≥ 10 mm	71 (2.9)	47 (2.4)	24 (5)	

SD- standard deviation

HGD – High-grade dysplasia

VA – Villous or tubulovillous adenoma

TA – Tubular adenoma

† Information available for 1740 patients (70.2%)

Table 2. Risk factors for advanced neoplasia at follow-up in multivariable analysis[§]

Factor	OR (95% CI)	*P* value
Age (yearly increment)*	1.05 (1.02-1.08)	0.001
Gender*		
Female	1	
Male	0.96 (0.58-1.56)	0.854
Time to follow-up (per year increment)*	1.06 (0.94-1.18)	0.353
Prep Quality*		
Poor/fair	1	
Excellent/Good	0.65 (0.32-1.31)	0.229
Indication*		
Screening	1	
Polyp surveillance	1.44 (0.84-2.47)	0.185
Diagnostic	0.81 (0.38-1.73)	0.581
Baseline adenoma findings*		
All adenomas ≤5 mm	1	
Any adenoma 6-9 mm	2.29 (1.38-3.80)	0.001
Baseline adenoma findings**		
1-2 adenomas both ≤ 5 mm	1	
1-2 adenomas one 6-9 mm	1.63 (0.78-3.39)	0.193
3-4 adenomas all ≤ 5 mm	0.94 (0.41-2.18)	0.889
3-4 adenomas one 6-9 mm	2.71 (1.14-6.43)	0.024
≥ 5 adenomas all ≤ 5 mm	0.99 (0.29-3.36)	0.992
≥ 5 adenomas one 6-9 mm	3.31 (1.51-7.28)	0.003

*Results from the first logistic regression

**Results from the second logistic regression. Results for age, gender, time to follow-up, bowel preparation quality and indication were nearly identical to the first analysis. Therefore, only the results for adenoma subgroups are shown for the second analysis

§ Logistic regression using enter method

OR – Odds ratio

Table 3. Advanced lesions at follow-up according to baseline colonoscopy findings

	1-2 both ≤ 5 mm	1-2 at least one 6-9 mm	3-4 all ≤ 5 mm	3-4 at least one 6-9 mm	5 or more all ≤ 5 mm	5 or more at least one 6-9 mm	*P* value
N	1625	272	271	102	101	106	
Male, n (%)	854 (53)	156 (57)	159 (59)	64 (63)	70 (69)	79 (75)	<0.001
Age, years (SD)	57.5 (9.7)	58.2 (9.5)	61.2 (8.8)	60.9 (9.7)	61.6 (8.8)	62.9 (9.3)	<0.001
Time to follow-up, years (SD)	4.7 (2.4)	4.1 (2.3)	4.3 (2.2)	3.9 (2.2)	3.5 (1.9)	2.9 (1.7)	<0.001
6 months – 1 year, n (%)	43 (2.6)	9 (3.3)	4 (1.5)	3 (2.9)	2 (2)	9 (8.5)	
1-3 years	321 (19.8)	68 (25)	56 (20.7)	28 (27.5)	36 (35.6)	45 (42.5)	
3-5 years	506 (31.1)	110 (40.4)	121 (44.6)	54 (52.9)	48 (47.5)	45 (42.5)	
5+ years	755 (46.5)	85 (31.3)	90 (33.2)	17 (16.7)	15 (14.9)	7 (6)	
Excellent/good bowel preparation, n (%)	982 (90)	161 (83)	182 (90.5)	65 (83.3)	78 (90.7)	84 (93.3)	0.019
Indication at baseline colonoscopy, n (%)							0.003
Screening	754 (46.4)	117 (43)	130 (48)	48 (47.1)	47 (46.5)	48 (45.3)	
Surveillance	480 (29.5)	79 (29)	95 (35.1)	29 (28.4)	39 (38.6)	45 (42.5)	
Diagnostic	391 (24.1)	76 (27.9)	46 (17)	25 (24.5)	15 (14.9)	13 (12.3)	
Patients with advanced neoplasms, n (%)	54 (3.3)	15 (5.5)	12 (4.4)	7 (6.9)	5 (5)	11 (10.4)	0.006†
Cancer	2 (0.1)	0	1 (0.4)	0	1 (1)	0	
HGD	4 (0.2)	1 (0.4)	1 (0.4)	0	0	1 (0.9)	
VA ≥ 10 mm	8 (0.5)	2 (0.7)	0	0	0	1 (0.9)	
VA < 10 mm	7 (0.4)	1 (0.4)	0	2 (2)	0	1 (0.9)	
TA ≥ 10 mm	33 (2)	11 (4)	13 (4.8)	5 (4.9)	4 (4)	8 (7.5)	

†Fisher exact test; SD – standard deviation; HGD – High-grade dysplasia; VA – Villous or tubulovillous adenoma; TA – Tubular Adenoma

Table 4. Advanced lesions among 6 baseline groups limited to screening indication only

	Baseline adenoma findings						
	1-2 both ≤ 5 mm	1-2 at least one 6-9 mm	3-4 all ≤ 5 mm	3-4 at least one 6-9 mm	5 or more all ≤5 mm	5 or more at least one 6-9 mm	*P* value
N	754	117	130	48	47	48	
Male, n (%)	416 (55.2)	77 (65.8)	79 (60.8)	32 (66.7)	34 (72.3)	39 (81.3)	0.001
Age, years (SD)	57.2 (8.2)	57.1 (8.1)	61.4 (7.9)	59.7 (7.9)	60.7 (7.9)	61.7 (7.4)	<0.001
Time to follow-up, years (SD)	5.1 (2.2)	4.5 (2.0)	4.8 (2.3)	4.2 (2.4)	3.6 (1.7)	3 (1.6)	<0.001
6 months-1year, n (%)	13 (1.7)	5 (4.3)	1 (0.8)	-	1 (2.1)	1 (2.1)	
1-3 years	91 (12.1)	15 (12.8)	16 (12.3)	14 (29.2)	14 (29.2)	14 (29.8)	
3-5 years	228 (30.2)	50 (42.7)	14 (29.2)	24 (50)	24 (50)	26 (55.3)	
5+ years	422 (56)	47 (40.2)	24 (50)	10 (20.8)	10 (20.8)	6 (12.8)	
Excellent/good bowel preparation, n (%)	525 (91)	85 (85.9)	96 (91.4)	35 (85.4)	36 (85.7)	38 (92.7)	0.377†
Patients with advanced neoplasms, n (%)	12 (1.6)	8 (6.8)	5 (3.8)	4 (8.3)	3 (6.4)	4 (8.3)	<0.001†
Cancer	-	-	-	-	1 (2.1)	-	
HGD	2 (0.3)	1	-	-	-	-	
VA ≥10 mm	-	-	-	-	-	-	
VA <10 mm	2 (0.3)	1 (0.9)	-	-	-	-	
TA ≥10 mm	8 (1.1)	6 (5.1)	5 (3.8)	4 (8.3)	2 (4.3)	4 (8.3)	

† Fisher exact
SD – Standard deviation
HGD – High-grade dysplasia
VA – Villous or tubulovillous adenoma
TA – Tubular adenoma

Table 5. Risk factors for advanced neoplasia (screening patients only) in multivariable analysis[§]

Factor	OR (95% CI)	*P* value
Age (yearly increment)	1.09 (1.04-1.13)	<0.001
Gender		
Female	1	
Male	0.89 (0.42-1.92)	0.774
Time to follow-up (per year increment)	1.06 (0.88-1.26)	0.553
Prep Quality		
Poor/fair	1	
Excellent/Good	0.62 (0.31-1.27)	0.191
Baseline adenoma findings		
1-2 adenomas both ≤ 5 mm	1	
1-2 adenomas one 6-9 mm	4.07 (1.50-11.04)	0.006
3-4 adenomas all ≤ 5 mm	1.12 (0.30-4.19)	0.861
3-4 adenomas one 6-9 mm	4.91 (1.44-16.75)	0.011
≥ 5 adenomas all ≤ 5 mm	3.24 (0.83-12.62)	0.091
≥ 5 adenomas one 6-9 mm	4.71 (1.30-17.05)	0.018

[§] Logistic regression using enter method

OR – Odds ratio

Table 6. Advanced lesions at follow-up according to baseline colonoscopy findings limited to patients with 1-2 adenomas at baseline whose follow-up colonoscopy was at 5±0.5 years.

	1-2 both ≤ 5 mm	1-2 at least one 6-9 mm	*P* value
N	461	53	
Male, n (%)	854 (53)	156 (57)	<0.001
Age, y (SD)	58.3 (9.1)	58.7 (9.1)	0.745
Time to follow-up, years (SD)	5.1 (0.2)	5.0 (0.2)	0.104
3-5 years, n (%)	128 (27.8)	20 (37.7)	
5+ years	333 (72.2)	33 (62.3)	
Excellent/good bowel preparation, n (%)	361 (96)	42 (93.3)	0.425†
Indication at baseline colonoscopy, n (%)			0.457
Screening	264 (57.3)	35 (66)	
Surveillance	116 (25.2)	10 (18.9)	
Diagnostic	81 (17.6)	8 (15.1)	
Patients with advanced neoplasms, n (%)	14 (3)	6 (11.3)	0.011†
Cancer	1 (0.2)	-	
HGD	2 (0.4)	1 (1.9)	
VA ≥ 10 mm	1 (0.2)	1 (1.9)	
VA < 10 mm	3 (0.7)	-	
TA ≥ 10 mm	7 (1.5)	4 (7.5)	

† Fisher exact

SD – Standard deviation

HGD – High-grade dysplasia

VA – Villous or tubulovillous adenoma

TA – Tubular adenoma

Table 7. Risk factors for advanced neoplasia at follow-up (limited to patients with 1-2 adenomas at baseline whose follow-up colonoscopy was at 5±0.5 years) in multivariable analysis[§]

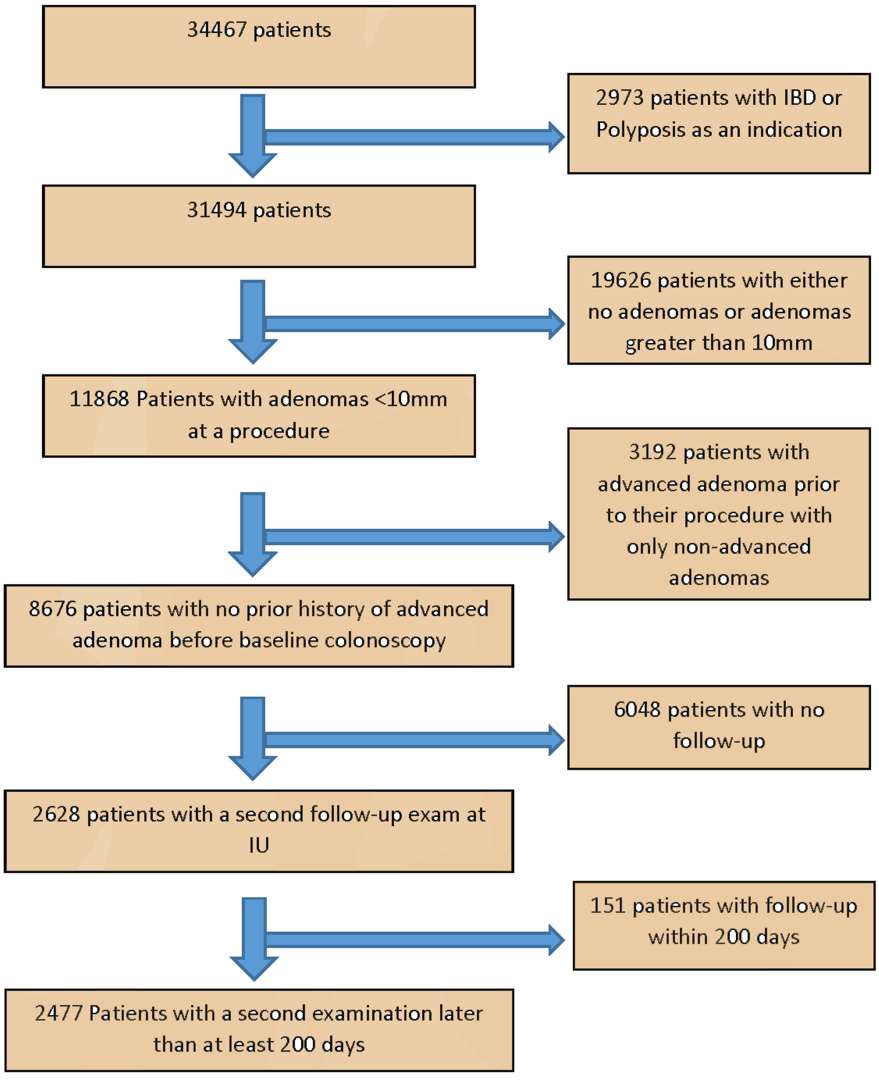
Factor	OR (95% CI)	*P* value
Age (yearly increment)	1.06 (0.99-1.13)	0.063
Gender		
Female	1	
Male	0.83 (0.26-2.73)	0.764
Time to follow-up (per year increment)	0.25 (0.02-4.07)	0.329
Prep Quality		
Poor/fair	1	
Excellent/Good	0.57 (0.06-5.87)	0.633
Indication		
Screening	1	
Polyp surveillance	1.8 (0.53-6.03)	0.344
Diagnostic	-	0.997
Baseline adenoma findings		
1-2 both ≤5 mm	1	
1-2 at least one 6-9 mm	5.23 (1.55-17.68)	0.008

[§] Logistic regression using enter method

OR – Odds ratio

Figure legend:

Figure 1. Patients excluded from the study


34467 patients
2973 patients with IBD or Polyposis as an indication
31494 patients
19626 patients with either no adenomas or adenomas greater than 10mm
11868 Patients with adenomas <10mm at a procedure
3192 patients with advanced adenoma prior to their procedure with only non-advanced adenomas
8676 patients with no prior history of advanced adenoma before baseline colonoscopy
6048 patients with no follow-up
2628 patients with a second follow-up exam at IU
151 patients with follow-up within 200 days
2477 Patients with a second examination later than at least 200 days

Acronyms and abbreviations

mm- millimeter

U.S.- United States

ADR- adenoma detection rate

HGD- high grade dysplasia

SSP- sessile serrated polyp

CD- cytological dysplasia

SD – standard deviation

VA – villous or tubulovillous adenoma

TA – tubular adenoma

OR- odds ratio

Supplementary Table 1. Advanced neoplasia according to baseline findings and including sessile serrated polyp (SSP) with cytological dysplasia and SSP ≥10 mm as advanced lesions.

	Patients with diminutive adenomas (1-5 mm) only	Patients with at least one small adenoma (6-9 mm)	*P* value
N	1997	480	
Age, years (SD)	58.3 (9.7)	59.8 (9.5)	0.002
Male gender (%)	1083 (54.2)	299 (62.3)	0.001
Time to follow-up examination, years (SD)	4.6 (2.4)	3.8 (2.2)	<0.001
6 months – 1 year, no. (%)	49 (2.5)	21 (4.4)	
1-3 years	413 (20.7)	141 (29.4)	
3-5 years	675 (33.8)	209 (43.5)	
5+ years	860 (43.1)	109 (22.7)	
Excellent or good bowel preparation†, n (%)	1242 (90.1)	310 (85.6)	0.014
Indication, n (%)			0.673
Screening	931 (46.6)	213 (44.4)	
Surveillance	614 (30.7)	153 (31.9)	
Diagnostic	452 (22.6)	114 (23.8)	
Advanced neoplasia at follow-up, n (%)	92 (4.6)	37 (7.7)	0.006
Cancer	4 (0.2)	-	
HGD or SSPCD	5 (0.3)	2 (0.4)	
VA ≥10 mm	8 (0.4)	3 (0.6)	
VA <10 mm	7 (0.4)	4 (0.8)	
TA or SSP ≥10 mm	68 (3.4)	28 (5.8)	

SD – Standard deviation

HGD – High-grade dysplasia

VA – Villous or tubulovillous adenoma

TA – Tubular adenoma

SSP – Sessile serrated adenoma/polyp

SSPCD – Sessile serrated polyp with cytological dysplasia

† Bowel preparation quality information available for 1740 of 2477 patients (70.2%)

Supplementary Table 2. Risk factors for advanced neoplasia according to baseline findings and including sessile serrated polyp (SSP) with cytological dysplasia and SSP ≥10 mm as advanced lesions in multivariable analysis[§]

Factor	OR (95% CI)	*P* value
Age (yearly increment)	1.04 (1.01-1.06)	0.004
Gender (male/female) Female Male	 1 0.79 (0.51-1.21)	0.281
Time to follow-up (per year increment)	1.02 (0.92-1.13)	0.756
Prep Quality Poor/fair Excellent/Good	 1 0.73 (0.39-1.40)	0.344
Indication Screening Polyp surveillance Diagnostic	 1 1.47 (0.91-2.38) 0.80 (0.41-1.55)	 0.113 0.506
Baseline adenoma findings All adenoma ≤5 mm Any adenoma 6-9 mm	 1 1.96 (1.24-3.117)	 - 0.004

[§] Logistic regression using enter method

OR – Odds ratio

Supplementary Table 3. Advanced neoplasia according to baseline findings and including sessile serrated polyp (SSP) with cytological dysplasia and SSP ≥10 mm as advanced lesions

	Baseline adenoma findings						
	1-2 both less than 6 mm	1-2 at least one 6-9 mm	3-4 all less than 6 mm	3-4 at least one 6-9 mm	5 or more all less than 6 mm	5 or more at least one 6-9 mm	*P* value
N	1625	272	271	102	101	106	
Male, n (%)	854 (53)	156 (57)	159 (59)	64 (63)	70 (69)	79 (75)	<0.001
Age, years (SD)	57.5 (9.7)	58.2 (9.5)	61.2 (8.8)	60.9 (8.7)	61.6 (8.8)	62.9 (9.3)	<0.001
Time to follow-up, years (SD)	4.7 (2.4)	4.1 (2.3)	4.3 (2.2)	3.9 (2.2)	3.5 (1.9)	2.9 (1.7)	<0.001
6 months-1year, no. (%)	43 (2.6)	9 (3.3)	4 (1.5)	3 (2.9)	2 (2)	9 (8.5)	
1-3 years	321 (19.8)	68 (25)	56 (20.7)	28 (27.5)	36 (35.6)	45 (42.5)	
3-5 years	506 (31.1)	110 (40.4)	121 (44.6)	54 (52.9)	48 (47.5)	45 (42.5)	
5+ years	755 (46.5)	85 (31.3)	90 (33.2)	17 (16.7)	15 (14.9)	7 (6)	
Excellent/good bowel preparation, n (%)	982 (90)	161 (83)	182 (90.5)	65 (83.3)	78 (90.7)	84 (93.3)	0.019
Indication at baseline colonoscopy, n (%)							0.003
Screening	754 (46.4)	117 (43)	130 (48)	48 (47.1)	47 (46.5)	48 (45.3)	
Surveillance	480 (29.5)	79 (29)	95 (35.1)	29 (28.4)	39 (38.6)	45 (42.5)	
Diagnostic	391 (24.1)	76 (27.9)	46 (17)	25 (24.5)	15 (14.9)	13 (12.3)	
Patients with advanced neoplasms, n (%)	71 (4.4)	17 (6.3)	15 (5.5)	7 (6.9)	6 (5.9)	13 (12.3)	0.014
Cancer	2 (0.1)	0	1 (0.4)	0	1 (1)	0	
HGD or SSPCD	4 (0.2)	1 (0.4)	1 (0.4)	0	0	1 (0.9)	
VA ≥ 10 mm	8 (0.5)	2 (0.7)	0	0	0	1 (0.9)	
VA < 10 mm	7 (0.4)	1 (0.4)	0	2 (2)	0	1 (0.9)	
TA OR SSP ≥ 10 mm	50 (3.1)	13 (4.8)	13 (4.8)	5 (4.9)	5 (5)	10 (9.4)	

SD – Standard deviation

HGD – High grade dysplasia

SSP – Sessile serrated polyp

SSPCD – Sessile serrated polyp with cytological dysplasia

VA – Villous or tubulovillous adenoma

Supplementary Table 4. Risk factors for advanced neoplasia according to baseline findings and including sessile serrated adenoma/polyp (SSP) with cytological dysplasia and SSP ≥10 mm as advanced lesions in multivariable analysis [§]

Factor	OR (95% CI)	*P* value
Age (yearly increment)	1.04 (1.01-1.06)	0.005
Gender		0.254
Female	1	
Male	0.78 (0.50-1.20)	
Time to follow-up (per year increment)	1.03 (0.92-1.14)	0.633
Prep Quality		
Poor/fair	1	
Excellent/Good	0.70 (0.37-1.34)	0.282
Indication		
Screening	1	
Polyp surveillance	1.46 (0.91-2.36)	0.121
Diagnostic	0.82 (0.42-1.59)	0.549
Baseline adenoma findings		
1-2 adenomas both ≤ 5 mm	1	-
1-2 adenomas with at least one 6-9 mm	1.44 (0.74-2.78)	0.284
3-4 adenomas all ≤ 5 mm	1.01 (0.50-2.06)	0.973
3-4 adenomas with at least one 6-9 mm	1.99 (0.86-4.62)	0.110
≥ 5 adenomas ≤ 5 mm	0.72 (0.22-2.41)	0.599
≥ 5 adenomas with at least one 6-9 mm	2.97 (1.45-6.08)	0.003

[§] Logistic regression using enter method

OR- Odds ratio

Supplementary Table 5. Advanced neoplasia according to baseline findings after removing 29 patients with > 10 adenomas at baseline

	Patients with diminutive adenomas (1-5 mm) only	Patients with at least one small adenoma (6-9 mm)	*P* value
N	1992	456	
Age, years (SD)	58.3 (9.7)	59.6 (9.3)	0.009
Male gender (%)	1080 (54.2)	280 (61.4)	0.005
Time to follow-up examination, years (SD)	4.6 (2.4)	3.8 (2.2)	<0.001
6 months -1year, n(%)	48 (2.4)	15 (3.3)	
1-3 years	409 (20.5)	129 (28.3)	
3-5 years	675 (33.9)	204 (44.7)	
5+ years	860 (43.2)	108 (23.7)	
Excellent or good bowel preparation, n (%)	1239 (90.2)	291 (85.1)	0.006
Indication, n (%)			0.760
Screening	928 (46.6)	205 (45.0)	
Surveillance	612 (30.7)	141 (30.9)	
Diagnostic	452 (22.7)	110 (24.1)	
Advanced neoplasia at follow-up (%)	71 (3.6)	31 (6.8)	0.002
Cancer	4 (0.2)	-	
HGD	5 (0.3)	2 (0.4)	
VA ≥ 10 mm	8 (0.4)	2 (0.4	
VA < 10 mm	7 (0.4)	4 (0.9	
TA ≥ 10 mm	47 (2.4	23 (5)	

SD – Standard deviation

HGD – High-grade dysplasia

VA – Villous or tubulovillous adenoma

TA – Tubular adenoma

Supplementary Table 6. Risk factors for advanced neoplasia according to baseline findings after removing 29 patients with more than 10 adenomas at baseline in multivariable analysis[§]

Factor	OR (95% CI)	*P* value
Age (yearly increment)	1.05 (1.03-1.08)	<0.001
Gender		
Female	1	
Male	0.93 (0.57-1.53)	0.783
Time to follow-up (per year increment)	1.06 (0.94-1.18)	0.354
Prep Quality		
Poor/fair	1	
Excellent/Good	0.64 (0.31-1.30)	0.214
Indication		
Screening	1	
Polyp surveillance	1.38 (0.80-2.37)	0.247
Diagnostic	0.80 (0.37-1.72)	0.566
Baseline findings		
All adenomas ≤5 mm	1	-
Any adenoma 6-9 mm	2.34 (1.40-3.91)	0.001

[§] Logistic regression using enter method

OR – Odds ratio

Supplementary Table 7. Advanced neoplasia according to baseline findings after removing 29 patients with more than 10 adenomas at baseline

	Baseline adenoma findings						
	1-2 both less than 6 mm	1-2 at least one 6-9 mm	3-4 all less than 6 mm	3-4 at least one 6-9 mm	5 or more all less than 6 mm	5 or more at least one 6-9 mm	*P* value
N	1625	272	271	102	96	82	
Male, n (%)	854 (53)	156 (57)	159 (59)	64 (63)	67 (70)	60 (73)	<0.001
Age, y (SD)	57.5 (9.7)	58.2 (9.5)	61.2 (8.8)	60.9 (8.7)	61.6 (8.8)	62.9 (9.3)	<0.001
Time to follow-up, years (SD)	4.7 (2.4)	4.1 (2.3)	4.3 (2.2)	3.9 (2.2)	3.6 (1.9)	3.1 (1.8)	<0.001
6 months-1year, n (%)	43 (2.6)	9 (3.3)	4 (1.5)	3 (2.9)	1 (1)	3 (3.7)	
1-3 years	321 (19.8)	68 (25)	56 (20.7)	28 (27.5)	32 (33.3)	33 (40.2)	
3-5 years	506 (31.1)	110 (40.4)	121 (44.6)	54 (52.9)	48 (50)	40 (48.8)	
5+ years	755 (46.5)	85 (31.3)	90 (33.2)	17 (16.7)	15 (15.6)	6 (7.3)	
Excellent/good bowel preparation, n (%)	982 (90)	161 (83)	182 (90.5)	65 (83.3)	75 (92.6)	65 (92.9)	0.018
Indication at baseline colonoscopy, n (%)							0.009
Screening	754 (46.4)	117 (43)	130 (48)	48 (47.1)	44 (45.8)	40 (48.8)	
Surveillance	480 (29.5)	79 (29)	95 (35.1)	29 (28.4)	37 (38.5)	33 (40.2)	
Diagnostic	391 (24.1)	76 (27.9)	46 (17)	25 (24.5)	15 (15.6)	9 (11)	
Patients with advanced neoplasms, n (%)	54 (3.3)	15 (5.5)	12 (4.4)	7 (6.9)	5 (5.2)	9 (11)	0.01†
Cancer	2 (0.1)	0	1 (0.4)	0	1 (1)	0	
HGD	4 (0.2)	1 (0.4)	1 (0.4)	0	0	1 (0.9)	
VA ≥ 10 mm	8 (0.5)	2 (0.7)	0	0	0	0	
VA < 10 mm	7 (0.4)	1 (0.4)	0	2 (2)	0	1 (1.2)	
TA ≥ 10 mm	33 (2)	11 (4)	10 (3.7)	5 (4.9)	4 (4.2)	7 (8.5)	

† Fisher exact

SD – Standard deviation

HGD – High grade dysplasia

VA – Villous or tubulovillous adenoma

TA – Tubular adenoma

Supplementary Table 8. Risk factors for advanced neoplasia according to baseline findings after removing 29 patients with > 10 adenomas at baseline in multivariable analysis[§]

Factor	OR (95% CI)	*P* value
Age (yearly increment)	1.05 (1.02-1.08)	<0.001
Gender		
Female	1	
Male	0.91 (0.55-1.50)	0.705
Time to follow-up (per year increment)	1.07 (0.95-1.19)	0.269
Prep Quality		
Poor/fair	1	
Excellent/Good	0.61 (0.30-1.25)	0.174
Indication		
Screening	1	
Polyp surveillance	1.37 (0.80-2.37)	0.255
Diagnostic	0.82 (0.38-1.77)	0.618
Baseline adenoma findings		
1-2 adenomas both ≤ 5 mm	1	-
1-2 adenomas one 6-9 mm	1.62 (0.78-3.38)	0.196
3-4 adenomas all ≤ 5 mm	0.93 (0.40-2.15)	0.864
3-4 adenomas one 6-9 mm	2.68 (1.13-6.37)	0.026
≥ 5 adenomas all ≤ 5 mm	1.05 (0.31-3.57)	0.935
≥ 5 adenomas one 6-9 mm	3.86 (1.70-8.77)	0.001

[§] Logistic regression using enter method

OR – Odds ratio